L8 ANSWER 33 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97011799 EMBASE
DOCUMENT NUMBER: 1997011799
TITLE: New prospects of ***targeting*** therapy for ***cancer*** .
AUTHOR: Tsujisaki M.; Sasaki S.; Imai K.
CORPORATE SOURCE: Dr. M. Tsujisaki, First Dept. of Internal Medicine, School of Medicine, Sapporo Medical University, Minami-1-jo, Nishi-16-chome, Chuo-ku, Sapporo 060, Japan
SOURCE: Biotherapy, (1996) 10/11 (1420-1428).
Refs: 26
ISSN: 0914-2223 CODEN: BITPE
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese
AB Molecular design with the use of biotechnology has enabled us to apply ***antibody*** related agents for ***cancer*** therapy: chimeric (humanized) monoclonal antibodies (MoAbs), bispecific antibodies, immunoconjugates and immunotoxins. A new strategy to develop MoAbs specific to biologically active molecules is discussed in this ***review*** , especially chimeric anti-erbB-2 MoAb, which may have the activity to induce apoptosis of ***cancer*** cells.

L8 ANSWER 34 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97011795 EMBASE
DOCUMENT NUMBER: 1997011795
TITLE: Immunotoxins.
AUTHOR: Ueda R.; Kawaguchi H.
CORPORATE SOURCE: Dr. R. Ueda, Second Dept. of Internal Medicine, Nagoya City University, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
SOURCE: Biotherapy, (1996) 10/11 (1392-1398).
Refs: 18
ISSN: 0914-2223 CODEN: BITPE
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
039 Pharmacy
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese
AB Monoclonal antibodies (MoAb) coupled to bacterial Mr plant toxins are termed immunotoxins. This is one strategy to ***target*** a cytotoxic agent to the ***cancer*** cells. First generation immunotoxins were made by chemically coupling MoAb to a native ***toxin*** , but this type of immunotoxin was too toxic due to nonspecific binding to normal tissues and to immunogenicity. To decrease the nonspecific toxicity, several modifications of immunotoxins were made, and genetic engineering was also used. By using recombinant DNA technique, it has been possible to produce recombinant toxins with better clinical properties and single chain immunotoxins, by fusing the DNA elements encoding combining regions of MoAb, growth factors, or cytokines to a ***toxin*** gene. This new generation of immunotoxins, namely recombinant immunotoxins, have more specific cytotoxicity for ***cancer*** cells with specific ligands and

less immunogenicity than the first ones. In this ***review*** , we will give an overview of the status of immunotoxins and recombinant immunotoxins in ***cancer*** therapy.

L8 ANSWER 35 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 11
ACCESSION NUMBER: 97027308 EMBASE
DOCUMENT NUMBER: 1997027308
TITLE: Immune response in ADEPT.
AUTHOR: Sharma S.K.
CORPORATE SOURCE: S.K. Sharma, CRC Clinical Research Laboratories, Dept. of Clinical Oncology, Royal Free Hosp. School of Medicine, Rowland Hill Street, London NW3 2PF, United Kingdom. sks@rfhsm.ac.uk
SOURCE: Advanced Drug Delivery Reviews, (1996) 22/3 (369-376). Refs: 55
ISSN: 0169-409X CODEN: ADDREP
PUBLISHER IDENT.: S 0169-409X(96)00440-1
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
023 Nuclear Medicine
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB ***Cancer*** therapy using murine monoclonal antibodies, radiolabelled as in radioimmunotherapy or conjugated to bacterial toxins or enzymes in ***antibody*** directed enzyme prodrug therapy (ADEPT) usually leads to the production of human anti-mouse antibodies (HAMA) and human anti-***toxin*** or human anti-enzyme antibodies in the patient. In most cases, this response interferes with the delivery of the ***antibody*** or the conjugate to the ***target*** and may also lead to adverse clinical side effects. The immune response to antibodies and enzymes may partly be avoided by use of humanised antibodies and human enzymes and immunosuppression. This chapter outlines some of the problems associated with the use of murine monoclonal antibodies conjugated to a bacterial enzyme and some of the approaches that have been studied to reduce the immunogenicity of proteins.

L8 ANSWER 36 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96077386 EMBASE
DOCUMENT NUMBER: 1996077386
TITLE: The use of immunoconjugates in ***cancer*** therapy.
AUTHOR: Ghetie M.-A.; Ghetie V.; Vitetta E.S.
CORPORATE SOURCE: Dept Microbiol/Cancer Immunobiol Ctr, Univ. Texas Southwestern Med. Center, 6000 Harry Hines,Dallas, TX 75235, United States
SOURCE: Expert Opinion on Investigational Drugs, (1996) 5/3 (309-321).
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
LANGUAGE: English

SUMMARY LANGUAGE: English

AB Those immunoconjugates that have entered clinical trials (i.e., immunotoxins, radiolabelled and bispecific antibodies) have shown promising antitumour activity in haematopoietic tumours (lymphomas/leukaemias). To eliminate large solid tumours, immunoconjugates will require changes in both the ***antibody*** and effector moieties since these tumours are poorly vascularised and rarely express tumour-specific antigens. This ***review*** describes improvements which may have a major impact on the next generation of immunoconjugates.

L8 ANSWER 37 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 12

ACCESSION NUMBER: 96077385 EMBASE

DOCUMENT NUMBER: 1996077385

TITLE: Development of produrgs for ADEPT ( ***antibody*** -direct enzyme prodrug therapy).

AUTHOR: Niculescu-Duvaz I.; Springer C.J.

CORPORATE SOURCE: Centre for Cancer Therapeutcs, Institute of Cancer Research, 15 Cotswold Road,Sutton, Surrey SM2 5NG, United Kingdom

SOURCE: Expert Opinion on Investigational Drugs, (1996) 5/3 (289-308).
ISSN: 1354-3784 CODEN: EOIDER

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB ***Antibody*** -Directed Enzyme Prodrug Therapy (ADEPT) is a ***targeting*** approach designed to improve the selectivity of anticancer drugs and to enable higher concentrations of drug to be generated at the ***target*** tumour than are currently possible with classical chemotherapy. ADEPT separates the cytotoxic from the ***targeting*** function of chemoimmunoconjugates in a multi-step system that has benefits over a one step chemo-, ***toxin*** - or radio-immunoconjugate. This ***review*** , whilst discussing the basic principles of ADEPT and the main requirements for all the components (enzymes, prodrugs and antibodies) of the systems, also summarises the latest results in the design and synthesis of prodrugs belonging to the main categories of anticancer compounds. The main features of ADEPT, such as ***targeting*** of ***cancer*** cells by the ***antibody*** -enzyme conjugates, enzymatic activation of the prodrugs, selection of the prodrug/drug and enzyme/prodrug systems are examined. A special emphasis has been placed on the prodrug/drug systems of potential clinical use, the rationale behind their design and the in vitro and in vivo results obtained with the different types of prodrugs. Analysis of ADEPT has indicated the potential for clinical use.

L8 ANSWER 38 OF 81 MEDLINE DUPLICATE 13

ACCESSION NUMBER: 1999035014 MEDLINE

DOCUMENT NUMBER: 99035014 PubMed ID: 9816166

TITLE: ***Antibody*** engineering of recombinant Fv immunotoxins for improved ***targeting*** of ***cancer*** : disulfide-stabilized Fv immunotoxins.

AUTHOR: Reiter Y; Pastan I

CORPORATE SOURCE: Laboratory of Molecular Biology, Division of Cancer Biology, Diagnosis, and Centers, National Cancer Institute, NIH, Bethesda, Maryland 20892-4255, USA.

SOURCE: CLINICAL CANCER RESEARCH, (1996 Feb) 2 (2) 245-52. Ref: 62
Journal code: C2H; 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990210



AB Recombinant immunotoxins are chimeric proteins in which a truncated ***toxin*** is fused to a recombinant antigen-binding domain such as a recombinant Fv or Fab. Recombinant immunotoxins ***target*** cell surface receptors and other antigens on tumor cells. The antigen-binding and - ***targeting*** domains in recombinant immunotoxins are usually single-chain Fvs (scFv), which are the ***antibody*** variable regions connected by a flexible peptide linker and fused directly to a bacterial ***toxin*** . However, Fabs have also been used. Recombinant immunotoxins have very good activity in vitro on cultured human tumor cell lines and have produced complete regressions and cures of established tumor xenografts in nude mouse models. Problems with the stability and binding of some scFv immunotoxins as well as scFvs not linked to ***toxin*** led to the development of a new type of recombinant Fv immunotoxin in which the ***targeting*** variable domains of the Fv are stabilized by an interchain disulfide bond located in structurally conserved framework positions of the VH and VL domains. These are termed disulfide-stabilized Fvs (dsFv) or dsFv immunotoxins. dsFvs and dsFv immunotoxins have several advantages over scFv immunotoxins. This ***review*** summarizes the design, construction, activities in vitro and in vivo, and biochemical characteristics of dsFv immunotoxins and compares them with scFv immunotoxins.

L8 ANSWER 39 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 14
ACCESSION NUMBER: 96078490 EMBASE
DOCUMENT NUMBER: 1996078490
TITLE: Novel genetic immunotoxins and intracellular antibodies for ***cancer*** therapy.
AUTHOR: Chen S.-Y.; Marasco W.A.
CORPORATE SOURCE: Department of Cancer Biology, Bowman Gray School of Medicine, Wake Forest University,Winston-Salem, NC 27157, United States
SOURCE: Seminars in Oncology, (1996) 23/1 (148-153).
ISSN: 0093-7754 CODEN: SOLGAV
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
022 Human Genetics
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English



AB In our recent studies we have developed two novel approaches with potential application for ***cancer*** therapy. One approach, termed genetic immunotoxins, is selectively ***targeted*** to the molecules on the cell surface to kill malignant cells. The genetic immunotoxin consists of an ***antibody*** -DNA- binding protein linked to a ***toxin*** expression plasmid DNA, and the selective cell killing of

the genetic immunotoxin is accomplished by transferring ***toxin*** expression DNAs into a ***target*** cell. The genetic immunotoxin with decreased immunogenicity and increased cytotoxicity may have significant advantages over currently described recombinant protein immunotoxins for ***cancer*** therapy. Another approach, termed intracellular antibodies, is ***targeted*** to inactivate an oncoprotein molecule inside cells to block the malignant growth by intracellular expression of engineered antibodies. We briefly illustrate the design of the two approaches and their potential for clinical applications.

L8 ANSWER 40 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96155113 EMBASE
DOCUMENT NUMBER: 1996155113
TITLE: Why toxins!.
AUTHOR: Fitzgerald D.
CORPORATE SOURCE: Laboratory of Molecular Biology, DBS, NCI, 37 Convent Drive,Bethesda, MD 20892-4255, United States
SOURCE: Seminars in Cancer Biology, (1996) 7/2 (87-95).
ISSN: 1044-579X CODEN: SECBE7
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Toxins are potent cytotoxic proteins which gain access to the interior of mammalian cells by receptor-mediated endocytosis. However the trafficking pathways within mammalian cells are complex and toxins must be processed to active forms while avoiding degradation, by the lysosomal system. Once delivered to an appropriate intracellular location, the active ***toxin*** fragment translocates to the cell cytosol and inhibits protein synthesis. Chimeric toxins are constructed by removing the toxins natural binding domain and replacing it with an ***antibody*** or cell-binding ligand that redirects cell killing activity to ***cancer*** cells. Gaining an understanding of how toxins manoeuvre within cells is vital for improving the effectiveness of chimeric toxins.

L8 ANSWER 41 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96133509 EMBASE
DOCUMENT NUMBER: 1996133509
TITLE: Immunotoxins: An update.
AUTHOR: Thrush G.R.; Lark L.R.; Clinchy B.C.; Vitetta E.S.
CORPORATE SOURCE: Department of Microbiology, Cancer Immunobiology Center, UT Southwestern Medical Center,Dallas, TX 75235, United States
SOURCE: Annual Review of Immunology, (1996) 14/- (49-71).
ISSN: 0732-0582 CODEN: ARIMDU
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The use of immunotoxins (ITs) in the therapy of ***cancer*** , graft-vs-host disease (GvHD), autoimmune diseases, and AIDS has been

QR180 .A5

ongoing for the past two decades. ITs contain a ***targeting*** moiety for delivery and a toxic moiety for cytotoxicity. Theoretically, one molecule of a ***toxin*** , routed to the appropriate cellular compartment, will be lethal to a cell. Newly developed MoAbs, toxins, and molecular biological technologies have enabled researchers to construct ITs that can effectively kill many different cell types. In fact, phase I/II clinical trials have given promising results. Although nonspecific toxicity and immunogenicity still limit the use of IT therapy, these agents hold enormous promise in an optimal setting to treat minimal disease.

L8 ANSWER 42 OF 81 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:531266 CAPLUS
DOCUMENT NUMBER: 125:211632
TITLE: Magic bullets. New directions for ***cancer*** therapy
AUTHOR(S): Taylerson, Chris
CORPORATE SOURCE: Department Biochemistry Molecular Biology, University College London, London, UK
SOURCE: Sci. Spectra (1996), 5, 24-29
CODEN: SCSPFE; ISSN: 1323-1413
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A ***review*** without refs. on hooking toxins to antibodies specific for ***cancer*** cells. Strategies for immunotherapy, immunotoxins, the ***targeting*** of ***cancer*** cells and the ***antibody*** -directed enzyme prodrug therapy (ADEPT) are described.

L8 ANSWER 43 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 15
ACCESSION NUMBER: 95367105 EMBASE
DOCUMENT NUMBER: 1995367105
TITLE: ***Antibody*** -Directed Enzyme Prodrug Therapy (ADEPT): A ***targeting*** strategy in ***cancer*** chemotherapy.
AUTHOR: Niculescu-Duvaz I.; Springer C.J.
CORPORATE SOURCE: CRC Centre for Cancer Therapeutics, Institute of Cancer Research, 15 Cotswold Road,Sutton, Surrey SM2 5NG, United Kingdom
SOURCE: Current Medicinal Chemistry, (1995) 2/3 (687-706).
ISSN: 0929-8673 CODEN: CMCHE7
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB ***Antibody*** -Directed Enzyme Prodrug Therapy (ADEPT) is a new conceptual approach designed to improve the selectivity of anti- ***cancer*** drugs. ADEPT separates the cytotoxic from the ***targeting*** function of immunoconjugates in a two phase system that has benefits over one phase chemo-, ***toxin*** - or radio-immunoconjugates. This ***review*** , while discussing the basic principles of ADEPT and the main requirements for all the components (enzymes, prodrugs and antibodies), of the systems, also summarizes the latest results obtained with this technology. The main components of ADEPT are described. These include the ***targeting*** of ***cancer*** cells by the ***antibody*** -enzyme conjugates, the enzymatic

activation of the prodrugs, the selection of the prodrug/drug (and/or enzyme/prodrug) systems. A special emphasis has been placed on the prodrug/drug systems, the rationale behind their design and the in vitro and in vivo results obtained with the different types of the prodrugs. The analysis of the advantages and disadvantages of the ADEPT system has led to the potential for clinical use of this system, which enables higher drug concentrations at the tumor compared to classical chemotherapy.

L8 ANSWER 44 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96061236 EMBASE
DOCUMENT NUMBER: 1996061236
TITLE: Tumour associated antigen specific antibodies: A tool for drug ***targeting*** in ***cancer*** .
AUTHOR: Venkatesan N.; Sood A.; Vyas S.P.
CORPORATE SOURCE: Dept. of Pharmaceutical Sciences,Sagar 470 003, India
SOURCE: Indian Drugs, (1995) 32/11 (510-519).
ISSN: 0019-462X CODEN: INDRBA
COUNTRY: India
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L8 ANSWER 45 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95159376 EMBASE
DOCUMENT NUMBER: 1995159376
TITLE: Immunotoxin therapy of ***cancer*** . Rationale for development and future potential.
AUTHOR: Bachier C.R.; LeMaistre C.F.
CORPORATE SOURCE: South Texas Cancer Institute, 7700 Floyd Curl Drive,San Antonio, TX 78229-3993, United States
SOURCE: Clinical Immunotherapeutics, (1995) 3/6 (450-460).
ISSN: 1172-7039 CODEN: CIMMEA
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Immunotoxin conjugates are potent cytotoxic agents. They are composed of toxins from plants or bacteria linked chemically or by protein engineering to antibodies or ligands that ***target*** cell surface structures present in malignant cells. Their cytoxicity is based on blocking protein synthesis. Studies in vitro and in animals have shown significant tumour cytotoxicity with minimal toxicity to normal tissues. Their novel mechanism of action, cell cycle independence, tumour specificity and low toxicity profile have made immunotoxins attractive candidates for use in clinical trials. Results from phase I/II studies of immunotoxins incorporating ricin, Pseudomonas exotoxin and diphtheria ***toxin*** have demonstrated the feasibility of this approach, especially in patients with leukaemias and lymphomas. Recent advances have made possible modifications in immunotoxin structure, resulting in even more potent and/or less immunogenic molecules. However, several obstacles must still be overcome such as: (a) immune-mediated neutralisation of the conjugate; (b) penetration of bulky tumours; and (c) intrinsic tumour resistance. Areas of future clinical investigation will include clinical trials with

newer conjugates, treatment of malignancies at a state of minimal disease, and combination of immunotoxins and other chemotherapeutic agents. These studies will define the role of immunotoxins in the therapy of ***cancer*** .

L8 ANSWER 46 OF 81 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:225437 CAPLUS
DOCUMENT NUMBER: 124:331285
TITLE: ***Targeted*** therapy of ***cancer*** and autoimmune diseases
AUTHOR(S): Press, Oliver W.; Wijdenes, John; Glennie, Martin J.; Bagshawe, Kenneth D.
CORPORATE SOURCE: Fred Hutchinson Cancer Research Center, University Washington, Seattle, USA
SOURCE: Pharmacol. Sci.: Perspect. Res. Ther. Late 1990s, [Int. Congr. Pharmacol.], 12th (1995), Meeting Date 1994, 381-9. Editor(s): Cuello, A. Claudio; Collier, Brian. Birkhaeuser: Basel, Switz.
CODEN: 62PPA6
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A ***review*** with 13 refs. ***Antibody*** -conjugates represent a promising new modality for refractory malignancies and autoimmune diseases that may afford greater selectivity and lesser toxicity than conventional cytotoxic treatments. Many types of immunoconjugates have been described including antibodies conjugated to conventional chemotherapeutic agents, plant toxins, bacterial toxins, radionuclides, and enzymes. We describe four promising new approaches. First, clin. trials employing unconjugated monoclonal antibodies ***targeting*** CD4 or the IL2 receptor are described for patients with autoimmune disorders such as rheumatoid arthritis, multiple sclerosis, and acute graft vs. host disease. Second, preclin. and clin. trials employing bispecific monoclonal antibodies recruiting the ***toxin*** , saporin, to idiotypic Igs or the CD22 antigen on B-cell lymphomas are discussed. Third, the use of ***antibody*** -enzyme conjugates in conjunction with prodrug substrates is presented. Finally, the use of radiolabeled anti-CD20 antibodies for treating patients with refractory B-cell lymphomas is summarized. Each of these methods has demonstrated impressive therapeutic results in preclin. models and clin. trials, warranting further investigation.

L8 ANSWER 47 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95083952 EMBASE
DOCUMENT NUMBER: 1995083952
TITLE: Immunotoxins as ***cancer*** chemotherapeutic agents.
AUTHOR: Siegall C.B.; Wolff E.A.; Gawlak S.L.; Paul L.; Chace D.; Mixan B.
CORPORATE SOURCE: Molecular Immunology Department, Bristol-Myers Squibb, Pharmaceutical Research Institute, 3005 First Avenue,Seattle, WA 98121, United States
SOURCE: Drug Development Research, (1995) 34/2 (210-219). ISSN: 0272-4391 CODEN: DDREDK
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

available on Admin.

SUMMARY LANGUAGE: English

AB Immunotoxins, composed of antibodies linked to protein toxins, are cell-specific cytotoxic reagents that have been constructed as both chemical conjugates and fusion proteins. A variety of different toxins derived from plants, such as ricin, saporin, and bryodin, and bacteria, including Diphtheria ***toxin*** and Pseudomonas exotoxin, have been utilized to construct extremely cytotoxic immunotoxin molecules. Single-chain immunotoxin fusion proteins composed of cloned ***antibody*** variable regions directly fused to toxins have several advantages over chemically conjugated forms, most importantly, enhanced in vivo antitumor activity. BR96 sFv-PE40 is a single-chain immunotoxin fusion protein that ***targets*** a Lewis-Y related antigen expressed on the surface of solid tumor cells. Complete regression and, in certain cases, cure of established tumor xenografts have been observed with BR96 sFv-PE40 administration into rodents. Clinical utility of immunotoxins has shown some promise but has been limited by many factors, most notably vascular leak syndrome (VLS). Our finding that rats serve as a model to study BR96 sFv-PE40 mediated VLS has led to identification of potential inhibitors of this dose-limiting toxicity. In summary, immunotoxins, especially single-chain forms, offer exciting possibilities for therapy of ***cancer*** .

L8 ANSWER 48 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 95336721 EMBASE

DOCUMENT NUMBER: 1995336721

TITLE: Recombinant immunotoxins: From basic research to ***cancer*** therapy.

AUTHOR: Brinkmann U.; Pastan I.

CORPORATE SOURCE: Laboratory of Molecular Biology, Division of Cancer Biology, National Cancer Institute, NIH, 9000 Rockville Pike,Bethesda, MD 20892, United States

SOURCE: Methods: A Companion to Methods in Enzymology, (1995) 8/2 (143-156).
ISSN: 1046-2023 CODEN: MTHDE

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Much work has been directed at the development of reagents that would combine the specificity of antibodies with potent and readily manipulated cytotoxic effector functions. In this ***review*** , we describe immunotoxins, molecules that contain an ***antibody*** -derived antigen binding region (Fv) coupled to a bacterial ***toxin*** , most commonly Diphtheria ***toxin*** or Pseudomonas exotoxin. Second-generation immunotoxins are fully recombinant fusion proteins containing a two-chain, disulfide-stabilized, or single-chain Fv region and a modified bacterial ***toxin*** . The relative advantages of the single-chain versus two-chain approach are described, as are techniques for purification of these agents from bacterial inclusion bodies. Finally, the use of such reagents as analytical tools in protein engineering and therapeutically, in ***cancer*** therapy, is discussed.

L8 ANSWER 49 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 95218711 EMBASE

DOCUMENT NUMBER: 1995218711
TITLE: Prospects for immunotoxin therapy of non-Hodgkin's lymphoma.
AUTHOR: Grossbard M.L.; Fidias P.
CORPORATE SOURCE: Hematology/Oncology Unit, Massachusetts General Hospital,Boston, MA 02114, United States
SOURCE: Clinical Immunology and Immunopathology, (1995) 76/2 (107-114).
ISSN: 0090-1229 CODEN: CLIIAT
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The use of unconjugated monoclonal antibodies to treat patients with non-Hodgkin's lymphoma by ***targeting*** specific antigenic determinants on malignant cells has been an area of intense laboratory and clinical research. Although occasional clinical successes have been seen, many limitations of such therapy have been identified, including the low endogenous cytotoxicity of most of the antibodies. More recently, investigators have attempted to employ monoclonal ***antibody*** - ***toxin*** conjugates (immunotoxins) to deliver specific cytotoxins to the lymphoma cell surface. This article describes the preclinical development of immunotoxin therapy as well as the initial results from selected Phase I and II clinical trials in patients with NHL. In addition, future directions are suggested for the use of these agents as adjuvant therapy and as treatment for patients with human immunodeficiency virus-related NHL.

L8 ANSWER 50 OF 81 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:594749 CAPLUS
DOCUMENT NUMBER: 121:194749
TITLE: ***Targeted*** toxins as anticancer agents
AUTHOR(S): Siegall, Clay B.
CORPORATE SOURCE: Department Molecular Immunology, Pharmaceutical Research Institute, Seattle, WA, 98121, USA
SOURCE: Cancer (Philadelphia) (1994), 74(3, SUPPL.), 1006-12
CODEN: CANCAR; ISSN: 0008-543X
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A ***review*** with 89 refs; transformed cells, such as those found in breast ***cancer*** , often overexpress a variety of cell surface receptors and antigens. Antibodies or growth factors that specifically recognize these membrane-bound structures can be linked with protein toxins, resulting in cell-specific cytotoxic reagents. Many of these cytotoxic mols. have been produced and are referred to as oncotoxins, mitotoxins, or immunotoxins, depending on the components of the chimeric mol. These bifunctional reagents are constructed as either chem. conjugates or fusion proteins between a ligand/ ***antibody*** and a ***toxin*** . This report focuses on the use of cytotoxic proteins ***targeted*** to epidermal growth factor receptors, fibroblast growth factor receptors, erbB-2/HER-2, and tumor-assocd. carbohydrate antigens. Using immunotoxin therapy, total regression of established tumors in animal xenograft models have been demonstrated. These results suggest that immunotoxin mols. offer exciting opportunities for the treatment of

human ***cancer*** .

L8 ANSWER 51 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94248142 EMBASE
DOCUMENT NUMBER: 1994248142
TITLE: Is there a role for immunoconjugates in the treatment of AIDS?.
AUTHOR: Pincus S.H.
CORPORATE SOURCE: NIAID Rocky Mountain Laboratories,Hamilton, MT 59840, United States
SOURCE: Expert Opinion on Investigational Drugs, (1994) 3/8 (799-807).
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The use of antibodies to deliver therapeutic agents to specific cells is a well-established concept in the treatment of malignancy. Therapeutic effects have been shown in both animal models and human clinical trials. By analogy, antibodies and other ligands may be used to treat AIDS by ***targeting*** cells that are actively producing HIV and spreading the infection. Immunoconjugates with specificity for HIV antigens or structures on the surface of HIV-infected cells have been made. These agents have undergone extensive in vitro testing. In tissue culture they can eliminate infected cells and halt the production of HIV. A number of agents have been shown to enhance the efficacy of anti-HIV immunoconjugates. Because animal models of HIV-infection are problematic, there has been little preclinical testing. Nevertheless, several clinical trials have begun.

L8 ANSWER 52 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94351470 EMBASE
DOCUMENT NUMBER: 1994351470
TITLE: Antibodies in the treatment of human ***cancer*** .
AUTHOR: Kuzel T.M.; Rosen S.T.
CORPORATE SOURCE: Division of Hematology/Oncology, Department of Medicine, Northwestern Univ. Medical School, 303 East Chicago Avenue,Chicago, IL 60611, United States
SOURCE: Current Opinion in Oncology, (1994) 6/6 (622-626).
ISSN: 1040-8746 CODEN: CUOOE8
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Monoclonal ***antibody*** -based therapy has the theoretic appeal of selective ***targeting*** of tumor cells. Most promising is the use of toxins and radioisotope immunoconjugates in the treatment of hematologic malignancies. Obstacles to effective treatment have been defined and

solutions are being pursued. The future use of this therapeutic strategy will be determined by creative approaches to enhance delivery, decrease immunogenicity, and maximize potency of ***antibody*** reagents.

L8 ANSWER 53 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94236664 EMBASE
DOCUMENT NUMBER: 1994236664
TITLE: Pharmacological modulation of peptide growth factor receptor expression on tumor cells as a basis for ***cancer*** therapy.
AUTHOR: Tagliaferri P.; Caraglia M.; Muraro R.; Pinto A.; Budillon A.; Zagonel V.; Bianco A.R.
CORPORATE SOURCE: Cattedra di Oncologia Medica, Facolta di Medicina, Universita 'Federico II' di Napoli, via S Pansini 5,80131 Naples, Italy
SOURCE: Anti-Cancer Drugs, (1994) 5/4 (379-393).
ISSN: 0959-4973 CODEN: ANTDEV
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Membrane receptors for peptide growth factor receptors (PGF-R) play a crucial role in the regulation of ***cancer*** cell proliferation and may behave as tumor associated antigens (TAA), which are currently regarded as specific ***targets*** for immunodetection and immunotherapy of human ***cancer*** . PGF-R are often more expressed by tumor cells than by normal counterparts and, by analogy to TAA, their surface expression may be regulated by cytokines. Moreover, the biological functions and specific ligands of most PGF-R are presently well elucidated as opposed to the great majority of TAA. PGF-R may, therefore, represent ideal cellular ***targets*** for at least two different therapeutic approaches: (i) naked or conjugated monoclonal antibodies and (ii) genetically engineered fusion proteins composed of PGF-R physiological ligands linked to genetically modified bacterial toxins. To date, clinical studies based on ***targeting*** of receptors for epidermal growth factor and interleukin-2 on tumor cells have been performed. Information from such studies suggests that PGF-R as well as TAA ***targeting*** strategies are clinically feasible, but that they still have to be optimized. A variety of host and tumor factors which affect ***targeting*** of neoplastic cells have been recently identified. For instance, it has been demonstrated that the antigenic density of the ***targeted*** molecule at the tumor cell surface is an important factor. In this view upregulation of PGF-R on ***cancer*** cells could be of major clinical advantage in immunotargeting. It has been reported that several cytokines and chemical compounds can induce PGF-R modulation on tumor cells. This paper reviews therapeutic opportunities related to the pharmacologic modulation of PGF-R expression. In addition a mechanistic hypothesis regarding PGF-R upregulation induced by cytostatic drugs and cytokines is proposed.

L8 ANSWER 54 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94135574 EMBASE
DOCUMENT NUMBER: 1994135574
TITLE: Delivery of drugs, proteins and genes into cells using transferrin as a ligand for receptor-mediated endocytosis.

AUTHOR: Wagner E.; Curiel D.; Cotten M.
CORPORATE SOURCE: Res. Institute Molecular Pathology, Dr. Bohr-Gasse 7,A-1030 Vienna, Austria
SOURCE: Advanced Drug Delivery Reviews, (1994) 14/1 (113-135). ISSN: 0169-409X CODEN: ADDREP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
016 Cancer
022 Human Genetics
026 Immunology, Serology and Transplantation
027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Transferrin, an iron-transporting serum glycoprotein, is efficiently taken up into cells by the process of receptor-mediated endocytosis. Transferrin receptors are found on the surface of most proliferating cells, in elevated numbers on erythroblasts and on many kinds of tumors. The efficient cellular mechanism for uptake of transferrin has been subverted for the delivery of low-molecular-weight drugs, protein toxins, and liposomes by linkage of these agents to transferrin or to anti-transferrin receptor antibodies. Linkage may be via chemical conjugation procedures or by the generation of chimeric fusion proteins. Transferrin conjugated to DNA-binding compounds (e.g. polycations or intercalating agents) has been successfully used for the import of DNA molecules into cells. High-level gene expression is obtained only if endosome-disruptive agents such as influenza hemagglutinin peptides or adenovirus particles are included which release the DNA complex from intracellular vesicles into the cytoplasm.

L8 ANSWER 55 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94044420 EMBASE
DOCUMENT NUMBER: 1994044420
TITLE: Immunotoxins: Is there a clinical value?.
AUTHOR: Gottstein C.; Winkler U.; Bohlen H.; Diehl V.; Engert A.
CORPORATE SOURCE: Onkologische Ambulanz, University of Cologne, Joseph-Stelzmannstr. 9,50924-Cologne, Germany
SOURCE: Annals of Oncology, (1994) 5/SUPPL. 1 (97-103). ISSN: 0923-7534 CODEN: ANONE2
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 016 Cancer
025 Hematology
037 Drug Literature Index
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Drug ***targeting*** is an attractive new approach to killing malignant cells, thereby leaving normal tissue unharmed. A decisive breakthrough was the advent of hybridoma technology, making monoclonal antibodies (MoAb) available in limitless supply. To construct reagents with selectivity for certain tumor cells, MoAbs or Fab' fragments were chemically linked to ribosome-damaging toxins derived from plants or bacteria like ricin, abrin, saporin, Pseudomonas exotoxin (PE), and diphtheria ***toxin*** (DT) to form immunotoxins, which combined the selectivity of the ***carrier*** moiety with the potency of the

***toxin*** moiety. The first generation of these immunotoxins showed impressive results in vitro but in most cases disappointing antitumour effects in animals or humans. By contrast, the second generation of immunotoxins, consisting of either A chain immunotoxins with a greatly improved stability in vivo or so-called 'blocked' ricin immunotoxins, have been demonstrated to be extremely effective in several animal models. Preliminary results of the current clinical trials suggest a possible clinical use of immunotoxins in leukemia and lymphoma patients. Genetically engineered fusion toxins have become available, which consist of a growth factor or a cytokine fused to a ***toxin*** moiety. In this paper, we will ***review*** the features of the three groups of immunotoxins which are most frequently used, i.e., ricin A chain and similar immunotoxins, blocked ricin immunotoxins, and recombinant toxins constructed with Pseudomonas exotoxin or diphtheria ***toxin*** .

L8 ANSWER 56 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 94051154 EMBASE
DOCUMENT NUMBER: 1994051154
TITLE: Immunotoxins and recombinant toxins in the treatment of solid carcinomas.
AUTHOR: Theuer C.P.; Pastan I.
CORPORATE SOURCE: Building 37, 9000 Rockville Pike,Bethesda, MD 20892, United States
SOURCE: American Journal of Surgery, (1993) 166/3 (284-288). ISSN: 0002-9610 CODEN: AJSUAB
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 009 Surgery
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB ***Cancer*** remains the second most common cause of death in our society, and advanced disease is often refractory to surgical, chemotherapeutic, and radiologic interventions. One novel approach to ***cancer*** treatment involves ***targeting*** a cytotoxic agent to a ***cancer*** cell. Immunotoxins have been developed that contain a potent ***toxin*** (either Pseudomonas exotoxin, ricin ***toxin*** , or diphtheria ***toxin*** ) coupled to a ***targeting*** moiety that directs the molecule to cells expressing a certain antigen. Chemically coupled immunotoxins have been developed over the past 12 years. These bind to and kill cells expressing many tumor-associated antigens. Initial clinical results were disappointing, but recent results have been more promising. Furthermore, newer immunotoxins have been developed that will soon be in clinical trials. Some of these are recombinant toxins that have been developed using techniques of genetic engineering. Transforming growth factor-.alpha., acidic fibroblast growth factor, insulin-like growth factor-1, interleukin-2, interleukin-4, interleukin-6, the binding portions of monoclonal antibodies, and CD4 have ben used to direct toxins to ***cancer*** cells or cells infected with the human immunodeficiency virus type 1. Efforts are under way to circumvent problems such as immunogenicity that may limit the clinical usefulness of immunotoxins.

L8 ANSWER 57 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93103684 EMBASE
DOCUMENT NUMBER: 1993103684
TITLE: Uses and limitations of monoclonal antibodies (MoAbs) in the treatment of malignant disease: A ***review*** .

AUTHOR: Kemshead J.T.; Hopkins K.
CORPORATE SOURCE: Imperial Cancer Research Fund, Paediatric/Neuro-Oncology Group, Frenchay Hospital,Bristol BS16 1LE, United Kingdom
SOURCE: Journal of the Royal Society of Medicine, (1993) 86/4 (219-224).
ISSN: 0141-0768 CODEN: JRSMD
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L8 ANSWER 58 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93003790 EMBASE
DOCUMENT NUMBER: 1993003790
TITLE: A role for gamma scintigraphy in ***cancer*** immunology and immunotherapy.
AUTHOR: Perkins A.C.; Pimm M.V.
CORPORATE SOURCE: Department of Medical Physics, University Hospital,Nottingham NG7 2UH, United Kingdom
SOURCE: European Journal of Nuclear Medicine, (1992) 19/12 (1054-1063).
ISSN: 0340-6997 CODEN: EJNMD
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
016 Cancer
023 Nuclear Medicine
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Facilities for radiolabelling and gamma scintigraphy are largely restricted to nuclear medicine departments or specialised research institutions and are therefore not widely available to workers in ***cancer*** research. Despite this, there is growing interest in gamma scintigraphy, which can provide information relevant to the entire field of ***cancer*** immunology. This ***review*** discusses the present and future roles of gamma scintigraphy in respect of ***antibody*** - ***targeted*** , cell-mediated and cytokine therapy. The authors aim to show that gamma scintigraphy is an investigative tool of great potential.

L8 ANSWER 59 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92174683 EMBASE
DOCUMENT NUMBER: 1992174683
TITLE: Cytotoxic conjugates containing translational inhibitory proteins.
AUTHOR: Ramakrishnan S.; Fryxell D.; Mohanraj D.; Olson M.; Li B.-Y.
CORPORATE SOURCE: Department of Pharmacology, University of Minnesota,Minneapolis, MN 55455, United States
SOURCE: Annual Review of Pharmacology and Toxicology, (1992) 32/- (579-621).
ISSN: 0066-4251 CODEN: ARPTDI
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 004 Microbiology
016 Cancer
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
052 Toxicology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L8 ANSWER 60 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92318931 EMBASE
DOCUMENT NUMBER: 1992318931
TITLE: Rational design of immunotoxins: Current progress and future prospects.
AUTHOR: Wawrzynczak E.J.
CORPORATE SOURCE: Drug Targeting Laboratory, Institute of Cancer Research,Sutton SM2 5NG, United Kingdom
SOURCE: Anti-Cancer Drug Design, (1992) 7/5 (427-441).
ISSN: 0266-9536 CODEN: ACDDEA
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Immunotoxins are hybrid protein molecules created by the chemical or genetic fusion of an ***antibody*** and a protein ***toxin*** . Advances in the molecular engineering of monoclonal antibodies and toxins now permit the generation of a variety of immunotoxin types with properties optimized for the therapy of different malignancies. Novel research promises a new generation of protein therapeutics in which the properties of intravascular transport, selective cell binding, internalization, translocation to the cytosol, subcellular localization and selective catalytic action can be manipulated to order. Immunotoxins that combine selective tumour binding with a tumour-specific mechanism of action, such as enzymatic inactivation of cellular products responsible for maintaining the malignant state, could have a potent and selective anti-tumour action.

L8 ANSWER 61 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92143985 EMBASE
DOCUMENT NUMBER: 1992143985
TITLE: Drug ***targeting*** with monoclonal antibodies: A ***review*** .
AUTHOR: Blakey D.C.
CORPORATE SOURCE: ICI Pharmaceuticals, Mereside, Alderley Park,Macclesfield, Chesire SK10 4TG, United Kingdom
SOURCE: Acta Oncologica, (1992) 31/1 (91-97).
ISSN: 0284-186X CODEN: ACTOEL
COUNTRY: Norway
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Monoclonal antibodies have been widely used in attempts to ***target*** anti-neoplastic agents selectively to tumours. Problems associated with

the use of monoclonal antibodies as the ***targeting*** moiety include lack of complete tumour selectivity, antigenic heterogeneity, tumour access and immunogenicity. Considerable effort in the ***targeting*** field is being expended in an attempt to reduce or overcome these problems. Attachment of monoclonal antibodies to low molecular weight cytotoxic drugs, protein toxins, radionuclides or enzymes capable of conversion of inactive prodrugs to cytotoxic drugs, has, despite these problems, resulted in conjugates which do have selective anti-tumour effects in animal models. The advantages and limitations of these different approaches are reviewed. It remains to be established in man if any of these approaches will result in significant therapeutic benefit in major solid tumours.

L8 ANSWER 62 OF 81 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:686989 CAPLUS
DOCUMENT NUMBER: 115:286989
TITLE: ***Targetting*** of anticancer agents
AUTHOR(S): Ikada, Yoshito
CORPORATE SOURCE: Fac. Eng., Kyoto Univ., Kyoto, 606, Japan
SOURCE: Kagaku (Kyoto) (1991), 46(10), 692-5
CODEN: KAKYAU; ISSN: 0451-1964
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A ***review*** with 13 refs. on drug ***targeting*** for ***cancer*** treatment including active ***targeting*** with immuotoxins and immunoconjugates, bonding of toxins to antibodies, in vivo animal and clin. exptl. results using the bound antibodies, passive ***targeting*** (immunotherapy) using biol. response modifiers, some aspects in their pharmaceutical formulations, and requirements in the ***targeting*** .

L8 ANSWER 63 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92047897 EMBASE
DOCUMENT NUMBER: 1992047897
TITLE: Prostatic polyamines and polyamine ***targeting*** as a new approach to therapy of prostatic ***cancer*** .
AUTHOR: Heston W.D.W.
CORPORATE SOURCE: Urologic Oncology Research Laboratory, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, United States
SOURCE: Cancer Surveys, (1991) 11/- (217-238).
ISSN: 0261-2429 CODEN: CASUD7
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The prostate is a rich factory of polyamine production. In spite of this, the prostate is also able to accumulate polyamines from the circulation. Intracellular polyamine depletion has been observed to enhance the accumulation of diamines such as putrescine. This needs to be taken advantage of either as a means for imaging prostatic tumour spread to the lymph nodes or as a means of ***targeting*** toxins to the prostatic tumour. Putrescine is a small molecule that may prove difficult for use for synthesizing stable ***toxin*** derivatives that can take advantage of the ***targeting*** potential of the polyamine

transporter. The cloning and sequencing characterization of the transporter is under way. When the prostatic transporter is identified, it will be possible to understand the role of the transporter in normal and cancerous prostatic cell growth and functioning and should serve to aid our understanding of how we can better optimize agents to use the transporter for delivery of antitumour agents.

L8 ANSWER 64 OF 81 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:622602 CAPLUS
DOCUMENT NUMBER: 115:222602
TITLE: Immunotoxins
AUTHOR(S): Press, Oliver W.
CORPORATE SOURCE: Dep. Med., Univ. Washington, Seattle, WA, USA
SOURCE: Biotherapy (Dordrecht, Neth.) (1991), 3(1), 65-76
CODEN: BTHREW
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A ***review*** with 58 refs. Immunotoxins (ITs) are chimeric mols. constructed by covalently conjugating monoclonal antibodies (MoAbs) to plant or bacterial toxins (e.g. ricin or pseudomonas exotoxin). The ***antibody*** moiety allows specific ***targeting*** of ITs to tumor-assocd. antigens, while the ***toxin*** moiety is responsible for cell killing by irreversible inactivation of protein synthesis. Since ITs must reach the cytosol to kill cells, the rates of endocytosis, the pathways of intracellular routing, and the rates of translocation to the cytoplasm are important determinants of the efficacy of an IT. Promising in vitro and in vivo IT results have been reported by many groups, and phase I clin. trials in ***cancer*** patients are currently underway.

L8 ANSWER 65 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 91095219 EMBASE
DOCUMENT NUMBER: 1991095219
TITLE: Ricin: a plant ***toxin*** with many potential therapeutic uses.
AUTHOR: Christiansen V.J.; Robinson C.P.
CORPORATE SOURCE: The University of Oklahoma, Health Sciences Center, 1110 Stonewall, Oklahoma City, OK 73190, United States
SOURCE: Drugs of the Future, (1991) 16/1 (53-61).
ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
031 Arthritis and Rheumatism
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L8 ANSWER 66 OF 81 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:597487 CAPLUS
DOCUMENT NUMBER: 115:197487
TITLE: Significance of immune conjugates in alternative ***cancer*** therapy
AUTHOR(S): Rosin, Thomas; Walzel, Hermann; Brock, Josef
CORPORATE SOURCE: Inst. Roentgendiagn., Bezirkskrankenhaus Poliklin. Rostock-Sued, Rostock, O-2500, Fed. Rep. Ger.
SOURCE: Wiss. Z. Univ. Rostock, Naturwiss. Reihe (1990), 39(4), 23-30
CODEN: WZUREU

DOCUMENT TYPE: Journal; General Review
LANGUAGE: German
AB A ***review*** , with 100 refs., describing the history, current status, and prospectives of alternative ***cancer*** chemotherapy, i.e. the ***targeted*** delivery of antineoplastic substances via immune-active carriers. Topics discussed include the coupling of drugs to monoclonal antibodies, enzymic-acting natural effector mols. (plant and bacterial proteins such as lectins) coupled to antibodies and the mechanisms of receptor-mediated endocytosis, the prepn. of such immunotoxins, and studies describing their activity in vitro, in vivo, and in clin. application.

L8 ANSWER 67 OF 81 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 90335273 MEDLINE
DOCUMENT NUMBER: 90335273 PubMed ID: 2198944
TITLE: Bifunctional antibodies: concept, production and applications.
AUTHOR: Nolan O; O'Kennedy R
CORPORATE SOURCE: School of Biological Sciences, Dublin City University, Glasnevin, Ireland.
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (1990 Aug 1) 1040 (1) 1-11. Ref: 59
Journal code: A0W; 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199009
ENTRY DATE: Entered STN: 19901012
Last Updated on STN: 19901012
Entered Medline: 19900907
AB Immunoglobulins, or antibodies, are monospecific, bivalent antigen-binding molecules. Bifunctional antibodies are bispecific, with each arm binding to a different antigen, and may be produced by biological or chemical methods. Biological production involves the fusion of two monoclonal ***antibody*** -producing hybridomas or of an immunised spleen cell and a hybridoma. The resulting hybrid hybridomas (quadromas or triomas) secrete a mixture of parenteral monoclonal antibodies and bifunctional ***antibody*** . In chemical production, the parental monoclonal antibodies can be 'chopped up and reconstituted' to produce the bifunctional ***antibody*** only. Bifunctional antibodies have a variety of potential uses. They were originally proposed as an aid to ***cancer*** chemotherapy where one of the arms of the ***antibody*** would bind to a tumour marker and the other to a drug, ***toxin*** , or cytotoxic cell. Functional agents can thus be ***target*** directly onto tumour cells, accumulating with higher density, yet with reduced side effects for the patient. Further applications have been proposed involving enzyme immobilization and novel immunoassay techniques. This ***review*** describes developments that have taken place in bifunctional ***antibody*** technology to date.

L8 ANSWER 68 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 90033787 EMBASE
DOCUMENT NUMBER: 1990033787
TITLE: Anti-idiotypic therapy of leukemias and lymphomas.
AUTHOR: Stevenson F.K.; George A.J.T.; Glennie M.J.
CORPORATE SOURCE: Lymphoma Research Unit, Tenovus Research Laboratory,

General Hospital,Southampton SO9 4XY, United Kingdom
SOURCE: Chemical Immunology, (1989) 48/- (126-166).
CODEN: CHMIEP
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Idiotypic determinants of the Ig expressed by the majority of B cell tumors present an attractive ***target*** for immunotherapeutic manipulations. The idiotypic Ig is molecularly defined and the behavior of the ***target*** cells placed under anti-idiotypic attack might have broader implications for ***cancer*** immunotherapy. Simple administration of monoclonal ***antibody*** reactive with these determinants clearly has only a limited effect on tumor load, due largely to the multiplicity of strategies by which the tumor cell can avoid such attack. These include modulation, change in idiotypic determinants due to somatic mutation, and complete loss of expression at the cell surface. If the first ***antibody*** treatment can be made more effective, for example by tailoring molecules to recruit available effector mechanisms more efficiently, or by the use of antibodies capable of delivering a lethal hit via a ***toxin*** , the tumor cell will presumably have less opportunity to escape. A second strategy is to immunize the tumor-bearing host with idiotypic Ig obtained from tumor cells. Once in place, such an immune response should suppress tumor growth on a continuing basis. In animal lymphoma, this approach appears to prolong survival although some of the escape mechanisms encountered for passive ***antibody*** therapy are apparently operative for active therapy. Study of these mechanisms should allow insight into how cells control expression of idiotypic determinants at the cell surface and open the possibility of further therapeutic intervention. A combined approach to the treatment of human lymphoma might be envisaged whereby tumor load is reduced by passive ***antibody*** , thus leaving the immune system relatively unscathed, and even perhaps releasing natural antitumor responses which could be further stimulated by immunization.

L8 ANSWER 69 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 88212295 EMBASE
DOCUMENT NUMBER: 1988212295
TITLE: Immunotoxins against solid tumors.
AUTHOR: Pirker R.
CORPORATE SOURCE: Second Medical Clinic, University of Vienna, A-1090 Vienna, Austria
SOURCE: Journal of Cancer Research and Clinical Oncology, (1988) 114/4 (385-393).
ISSN: 0171-5216 CODEN: JCROD7
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 010 Obstetrics and Gynecology
016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB ***Antibody*** - ***toxin*** conjugates, termed immunotoxins, are currently being evaluated as potential new anticancer agents. The

monoclonal antibodies that recognize antigens on the surface of tumor cells should deliver the toxins or the catalytic subunits of toxins to ***cancer*** cells. The catalytically active parts of the immunotoxins have to reach the cell cytoplasm where they inhibit protein synthesis. Immunotoxins against various solid tumors, including breast carcinoma and ovarian carcinoma, have been developed. In vitro, the activity of immunotoxins is affected by the number of ***target*** antigens on the cell surface, the internalization of the immunotoxins, the kind of ***toxin*** , the class of the ***antibody*** , the kind of linkage, and by other factors. Several problems arise with in vivo administration of immunotoxins. The short serum half-life of immunotoxins, due to their rapid hepatic uptake, decreases the number of immunotoxin molecules that reach the solid tumor. This, together with low tumor penetration by immunotoxins, could lead to low anti-tumor activity. Heterogeneity of tumors, immunogenicity of immunotoxins, and cross-reactivity of immunotoxins with normal tissues are other factors that might limit the clinical use of immunotoxins. It should be possible, however, to overcome these problems using methods that are already available or have yet to be developed.

L8 ANSWER 70 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 89068719 EMBASE
DOCUMENT NUMBER: 1989068719
TITLE: Immunotoxins: Properties, applications and current limitations.
AUTHOR: Lord J.M.; Spooner R.A.; Hussain K.; Roberts L.M.
CORPORATE SOURCE: Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, United Kingdom
SOURCE: Advanced Drug Delivery Reviews, (1988) 2/3 (297-318).
ISSN: 0169-409X CODEN: ADDREP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
026 Immunology, Serology and Transplantation
030 Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Immunotoxins are conjugates in which monoclonal antibodies or their fragments are linked, normally via a disulfide bond, to eiter holotoxins or their toxic subunits. If the monoclonal ***antibody*** is cell-type-specific for a surface antigen, the immunotoxin should by cytotoxic to the antigen-bearing cells but not to other cell types. In general, while immunotoxins containing whole toxins exhibit greater cytotoxicity than immunotoxins lacking a ***toxin*** cell-binding polypeptide, their ***target*** cell specificity is inevitably reduced. The usefulness and limitations of current construct are discused, together with the prospects for developing immunotoxins with improved therapeutic potential using recombinant DNA techniques.

L8 ANSWER 71 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 88277662 EMBASE
DOCUMENT NUMBER: 1988277662
TITLE: Serotherapy of ovarian ***cancer*** .
AUTHOR: Lidor Y.; Bast Jr. R.C.
CORPORATE SOURCE: Department of Medicine, Duke University Medical Center, Durham, NC 27710, United States
SOURCE: Natural Immunity and Cell Growth Regulation, (1988) 7/4 (193-215).
ISSN: 0254-7600 CODEN: NICRDR

COUNTRY: Switzerland
DOCUMENT TYPE: Journal
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The development of monoclonal antibodies has permitted the identification of several ovarian-tumor-associated antigens which might serve as ***targets*** for serotherapy in vivo. With the exception of antibodies directed against growth factor receptors, unmodified monoclonal reagents must activate complement (C') components or bind effector cells to destroy tumor ***targets*** . ***Antibody*** -dependent cell-mediated cytotoxicity (ADCC) may be particularly important for eliminating tumor cells in vivo. A shortage of functionally active effector cells can limit the efficacy of serotherapy with heteroantisera or monoclonal reagents. The use of immunostimulants such as Corynebacterium parvum has increased the number and activity of effector cells for ADCC within the peritoneal compartment of mice and of patients with ovarian ***cancer*** . Intraperitoneal serotherapy can achieve direct contact between ***antibody*** and microscopic deposits of ovarian tumor cells which persist following cytoreductive operations and cytotoxic chemotherapy. Conjugation of monoclonal antibodies with radionuclides, drugs or toxins might increase the potency of serotherapy and circumvent the effector shortage. Clinical studies to date have evaluated radionuclide conjugates for imaging and for therapy. Patients with a small volume of disease have responded to treatment. Preclinical models suggest that drug and ***toxin*** conjugates might also prove active. Recent studies have demonstrated a synergistic interaction between different immunotoxins. Ovarian carcinoma is likely to be a valuable clinical model for evaluating immunoconjugates which react with epithelial tumor cells.

L8 ANSWER 72 OF 81 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1989:470159 CAPLUS
DOCUMENT NUMBER: 111:70159
TITLE: The potential of membrane-acting toxins for ***targeted*** ***cancer*** therapy
AUTHOR(S): Drobniewski, Francis A.; Thorpe, Philip E.; Wallace, Philip M.; Wawrzynczak, Edward J.
CORPORATE SOURCE: Drug Target. Lab., Imp. Cancer Res. Fund, London, WC2A 3PX, UK
SOURCE: NATO ASI Ser., Ser. A (1988), 155(Targeting Drugs: Anat. Physiol. Consid.), 103-8
CODEN: NALSDJ
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A ***review*** with 20 refs. The potentials of ***targeting*** surface-active toxins (cytolysins) with monoclonal antibodies for ***cancer*** therapy are discussed.

L8 ANSWER 73 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 88015011 EMBASE
DOCUMENT NUMBER: 1988015011
TITLE: Monoclonal antibodies in ***cancer*** diagnosis and therapy.
AUTHOR: Reilly R.; Sheldon K.
CORPORATE SOURCE: Nuclear Medicine Department, The Princess Margaret Hospital, Toronto, Ont., Canada
SOURCE: Canadian Journal of Hospital Pharmacy, (1987) 40/6 ( 209-214).

CODEN: CJHPAV
COUNTRY: Canada
DOCUMENT TYPE: Journal
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In 1975 Georges Kohler and Cesar Milstein revolutionized the field of immunology with their report on the development of a technique to produce a single ***antibody*** of constant specificity and affinity known as a monoclonal ***antibody*** . Since then a number of monoclonal antibodies to tumour-associated antigens have been developed. Considerable interest has been expressed in using these antibodies to selectively ***target*** radionuclides, cell toxins or chemotherapeutic drugs to human tumours for diagnostic or therapeutic purposes. While initial studies in animals and patients look very promising, several problems and issues affecting their use have become apparent. This ***review*** discusses these problems and issues, in particular: tumour antigens and antigen heterogeneity, circulating antigen, cross-reactivity with normal tissues, tumour characteristics, ***antibody*** characteristics, human anti-mouse antibodies, whole ***antibody*** versus fragments and the selection of the radiolabel for radionuclide labelled antibodies. For ***toxin*** -conjugated antibodies the issue of A-chain versus intact immunotoxins is discussed and for chemotherapeutic drug-conjugated antibodies the problem of the level of drug conjugation, specificity and drug resistance are described.

L8 ANSWER 74 OF 81 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1988:146453 BIOSIS
DOCUMENT NUMBER: BR34:71530
TITLE: MONOCLONAL ***ANTIBODY*** ***TARGETING*** FOR ***CANCER*** IMMUNOTHERAPY.
AUTHOR(S): EMBLETON M F; BALDWIN R W
CORPORATE SOURCE: CANCER RES. CAMPAIGN LAB., UNIV. NOTTINGHAM, UNIVERSITY PARK, NOTTINGHAM NG7 2RD, UK.
SOURCE: BIENVENU, J., J. A. GRIMAUD AND P. LAURENT (ED.). MARKER PROTEINS IN INFLAMMATION PROCEEDINGS, VOL. 3; SYMPOSIUM, LYON, FRANCE, JUNE 26-28, 1985. XV+693P. WALTER DE GRUYTER: BERLIN, WEST GERMANY; NEW YORK, NEW YORK, USA. ILLUS, (1986) 0 (0), 529-542.
ISBN: 3-11-010639-6, 0-89925-223-0.
FILE SEGMENT: BR; OLD
LANGUAGE: English

L8 ANSWER 75 OF 81 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1986:583250 CAPLUS
DOCUMENT NUMBER: 105:183250
TITLE: Monoclonal ***antibody*** ***targeting*** for ***cancer*** immunotherapy
AUTHOR(S): Embleton, M. J.; Baldwin, R. W.
CORPORATE SOURCE: Cancer Res. Campaign Lab., Univ. Nottingham, Nottingham, NG7 2RD, UK
SOURCE: Marker Proteins Inflammation (1986), 3, 529-42
CODEN: MPINEG
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A ***review*** with 46 refs. Monoclonal ***antibody*** - ***toxin*** conjugates and ***antibody*** -drug conjugates are

discussed.

L8 ANSWER 76 OF 81 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:400006 CAPLUS
DOCUMENT NUMBER: 107:6
TITLE: ***Antibody*** ***targeting*** of ***toxin*** polypeptides
AUTHOR(S): Frankel, A. E.; Bjorn, M. J.; Winkelhake, J. L.
CORPORATE SOURCE: Dep. Protein Chem., Cetus Corp., Emeryville, CA, 94608, USA
SOURCE: Protein Eng. (1986), 351-63. Editor(s): Inouye, Masayori; Sarma, Raghupathy. Academic: Orlando, Fla. CODEN: 55PBA8
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A ***review*** with 94 refs. of immunotoxins, with emphasis on the prepn. and reactivity of immunotoxins with breast ***cancer*** cells.

L8 ANSWER 77 OF 81 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:522417 CAPLUS
DOCUMENT NUMBER: 101:122417
TITLE: Biochemical aspects of ***antibody*** -directed delivery of toxins and drugs to ***target*** ***cancer*** cells
AUTHOR(S): Chersi, A.
CORPORATE SOURCE: Ist. Regina Elena Cancer Res., Rome, Italy
SOURCE: J. Exp. Clin. Cancer Res. (1984), 3(3), 217-23 CODEN: JECRDN
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A ***review*** with 25 refs.

L8 ANSWER 78 OF 81 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:470527 CAPLUS
DOCUMENT NUMBER: 101:70527
TITLE: Immunotoxins
AUTHOR(S): Collier, R. John; Kaplan, Donald A.
CORPORATE SOURCE: Dep. Microbiol., UCLA, Los Angeles, CA, USA
SOURCE: Sci. Am. (1984), 251(1), 56-64 CODEN: SCAMAC; ISSN: 0036-8733
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A ***review*** with no refs. of using toxins conjugated to tumor antigen-specific monoclonal antibodies to destroy ***targeted*** ***cancer*** cells.

L8 ANSWER 79 OF 81 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1984:66589 BIOSIS
DOCUMENT NUMBER: BR26:66589
TITLE: LINKAGE OF CYTO TOXIC AGENTS TO IMMUNO GLOBULINS.
AUTHOR(S): BLAIR A H; GHOSE T I
CORPORATE SOURCE: DEP. BIOCHEM., FACULTY MED., DALHOUSIE UNIV., COLLEGE ST., HALIFAX, NOVA SCOTIA B3H 4H7, CANADA.
SOURCE: J. Immunol. Methods, (1983) 59 (2), 129-144. CODEN: JIMMBG. ISSN: 0022-1759.
FILE SEGMENT: BR; OLD
LANGUAGE: English

L8 ANSWER 80 OF 81 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 82131747 EMBASE
DOCUMENT NUMBER: 1982131747
TITLE: Immunotoxins: Hybrid molecules combining high specificity and potent cytotoxicity.
AUTHOR: Jansen F.K.; Blythman H.E.; Carriere D.; et al.
CORPORATE SOURCE: Cent. Rech. Clin-Midy, 34082 Montpellier, France
SOURCE: Immunological Reviews, (1982) Vol. 62/- (185-216).
CODEN: IMRED2
COUNTRY: Denmark
DOCUMENT TYPE: Journal
FILE SEGMENT: 026 Immunology, Serology and Transplantation
016 Cancer
037 Drug Literature Index
LANGUAGE: English

AB With the aim of constructing ***antibody*** - ***toxin*** conjugates in which the ***toxin*** part should be inactive during the transport and only become active after the binding of the ***antibody*** to its ***target*** , we coupled the toxic A-chain of ricin to different antibodies. A-chain without a binding site seemed to fulfil these requirements. The A-chain alone has only a low in vitro and in vivo toxicity. Only a dose corresponding to the LD50 (about 460 micrograms per mouse) affects the crypts of Lieberkuhn, liver parenchyma and the tubules of the kidney. Conjugates between A-chain and antibodies which may be called A-chain immunotoxins (a-IT) became highly specific and efficient for their ***target*** tumor cells if the following conditions were met: extreme purification of A-chain to eliminate trace amounts of B-chain contamination, a labile disulfide bridge and a method which couples A-chain to ***antibody*** without denaturation, purified antibodies of high affinity, and potentiation of IT activity by ammonium chloride. Such IT have several advantages in vitro, since they are immunologically specific, highly efficient, able to kill the last plated tumor cells, highly reproducible, and stable at -20.degree.C. Their limitations are a relative cellular resistance to IT, depending on the cell line, a potency which is only sometimes higher than complement-dependent lysis, slow kinetics, and a decrease of potency under more physiological in vitro conditions. In vivo IT, similar to A-chain, (LD50, 23.3 mg/kg) is not very toxic and has a half-life of about 30 min in the mouse. Tumor growth of TNP-HeLa cells could be significantly inhibited with an IT against DNP. The life-span of mice injected with TNP-L1210 cells was also significantly prolonged with a similar IT. An anti-Thy 1.2 IT, however, produced only slight tumor inhibition. A clinical administration of IT may be envisaged, after more intensive animal experiments, in patients with only a few residual tumor cells, i.e. in the remission phase in order to kill the last tumor cells by this different approach. An immediate use of IT, however, could be an in vitro destruction of tumor cells present in the autologous bone marrow of leukemia patients. After a supralethal treatment of these patients with drugs or X-ray irradiation they could then be retransplanted with their own bone marrow, which should now be free of tumor cells.

L8 ANSWER 81 OF 81 EMBASE 
ACCESSION NUMBER: 82202771 EMBASE
DOCUMENT NUMBER: 1982202771
TITLE: Chimeric toxins.
AUTHOR: Olsnes S.; Pihl A.
CORPORATE SOURCE: Norsk Hydro's Inst. Cancer Res., Montebello, Oslo, Norway
SOURCE: Pharmacology and Therapeutics, (1981) 15/3 (355-381).
CODEN: PHTHDT
COUNTRY: United Kingdom

DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
LANGUAGE: English

AB In spite of tremendous efforts to develop agents suitable for chemical treatments of ***cancer*** the success has so far been limited. None of the cytotoxic agents in current use act specifically on ***cancer*** cells, and a great deal of work has been aimed at increasing the specificity of the drugs. It is now recognized that the high specificity of hormones and certain drugs involves their recognition and interaction with specific receptors on the cell surface or in the cytosol of the ***target*** cells. The interaction of a specific ***antibody*** with its antigen on the cell surface is also highly specific. For this reason many attempts have been made in recent years to utilize the selectivity of hormones and antibodies to direct various cytotoxic agents to defined groups of cells. A number of toxic proteins owe their extreme potency to the fact that they possess an enzymatically active A-chain which exerts the toxic effect, and one or more B-chains which bind the toxins to cell surface receptors. Due to the enzymatic activity of the A-chain the presence in the cytosol of a single A-chain is sufficient to kill a cell. Since receptors for the B-chain of these toxins are present on the surface of most cells of sensitive animals, the unmodified toxins show little selective toxicity. In recent years many workers have explored the possibility of replacing the binding moieties of the toxins with other binding moieties having a different specificity. As new binding moieties, lectins, protein hormones or their subunits, and antibodies or their fragments have been used. The availability of monoclonal antibodies has greatly increased the interest in this approach and currently a number of laboratories are involved in constructing hybrid or chimeric toxins, consisting of the enzymatically active moiety of such a protein ***toxin*** , linked to a binding moiety derived from a different source. Such chimeric toxins not only may have a high cell specificity, but they also have the added advantage that if the complexes are degraded and the enzymatically active A-chains are released, they are virtually non-toxic to cells. This is in contrast to conjugates involving conventional cytotoxic agents. If these are released from the complexes they will act non-specifically. The present ***review*** will be restricted to chimeric toxins involving the enzymatically active part of protein toxins.